Protocol GTC-36-301: An Open Label, Cross-over Study of Renagel® and Calcium Acetate in Hemodialysis Patients.

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Name of Sponsor/Company

Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142
Geltex Pharmaceuticals, Inc., Waltham, MA 02451, (Geltex Pharmaceuticals, Inc. was acquired by Genzyme Corporation December 2000)

Investigators and Study Center(s)

This was a multicenter study conducted at 8 sites in the United States.

Studied Period

First patient entered: 8 July 1996
Last patient completed: 10 February 1997

Phase of Development

Phase 3

Objectives
Primary

- Determine the efficacy of Renagel® in lowering serum phosphorus in hemodialysis patients
- Determine the safety of Renagel® in lowering serum phosphorus in hemodialysis patients

Secondary:

- Compare the efficacy of Renagel® and calcium acetate in lowering serum phosphorus in hemodialysis patients
- Compare the safety of Renagel® and calcium acetate in hemodialysis patients
- Compare the effects of Renagel® and calcium acetate on lipid profiles in hemodialysis patients
- Determine the effects of Renagel® and calcium acetate on intact parathyroid hormone levels in hemodialysis patients

Methodology

This was a phase 3, multi-center, open label, cross-over study. Patients were randomly assigned to one of two sequence groups. Following a two-week phosphate binder washout, the sequence 1 group was treated with Renagel® for eight weeks and then was crossed over to calcium acetate for another eight weeks of therapy. The sequence 2 group was treated with calcium acetate for eight weeks and then crossed over to Renagel® for another eight weeks of therapy. There was a two-week washout between treatments and a two-week washout following the second active treatment period. The entire study lasted 22 weeks.

Number of Patients (Planned and Analyzed)

No. Enrolled / Treated: 109/84
No. Completed: 75

Diagnosis and Main Criteria for Inclusion

Adult men or women on a stable three-times weekly hemodialysis regimen and a stable phosphate binder regimen.

Test Product, Dose, and Mode of Administration

Sevelamer hydrochloride (Renagel®): 465 mg capsules (440 mg anhydrous)

Starting dose was determined based on the initial degree of hyperphosphatemia and ranged from 2 to 4 capsules three times per day with meals.

Administered orally with meals

Duration of Treatment

The total study duration was 22 weeks. Patients were treated with Renagel® for eight weeks and calcium acetate for eight weeks.

Reference Therapy, Dose and Mode of Administration

Calcium acetate (PhosLo®) : 667 mg tablets

Starting dose was determined based on the initial degree of hyperphosphatemia and ranged from 1 to 3 tablets three times per day with meals.

Administered orally with meals

CRITERIA FOR EVALUATION
Efficacy

The primary efficacy analysis is based on the change in serum phosphorus during the Renagel® treatment period.

Secondary analyses included the comparison of the changes in serum phosphorus, intact parathyroid hormone and serum lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) during both treatment periods.

Safety

Safety was evaluated on the basis of adverse experiences and changes in laboratory values.

STATISTICAL METHODS
Efficacy

All statistical analyses are based on two-tailed hypotheses tests with a significance level of 0.05.

Change in serum phosphorus: Results were summarized for the changes in serum phosphorus between baseline and the end of each study period. Wilcoxon signed rank tests were used to assess the changes. An ANOVA model was used to assess sequence, treatment, and sequence-by-treatment interactions.

Change in serum calcium: Results were summarized for all study visits and for the changes in serum calcium between baseline and the end of each study period. Wilcoxon signed rank tests were used to assess the changes. The Wilcoxon signed rank test was used to compare baseline values within a sequence to indicate whether there is a significant carry-over effect within a sequence. An ANOVA model was used to assess sequence, treatment, and sequence-by-treatment interactions.

Hypercalcemia was defined as serum calcium levels greater than or equal to 10.4 mg/dL. Modifications to the statistical plan included additional analysis performed for hypercalcemic events defined as serum calcium levels greater than or equal to 11.0 mg/dL. The proportion of patients with hypercalcemic events by week was summarized for both the washout and

treatment periods. McNemar's paired comparison test was used to compare the incidence of hypercalcemia for the two treatment groups.

Change in intact parathyroid hormone: Results were summarized for all study visits and for the changes in serum PTH between baseline and the end of each study period. Wilcoxon signed rank tests were used to assess the changes. An ANOVA model was used to assess sequence, treatment, and sequence-by-treatment interactions.

Change in lipids: Results were summarized for all study visits and for the changes in serum lipids between baseline and the end of each study period. Wilcoxon signed rank tests were used to assess the changes. An ANOVA model was used to assess sequence, treatment, and sequence-by-treatment interactions.

Safety

Adverse experiences: The frequency and percent of patients and the frequency of events were presented for treatment emergent adverse events, for those events judged by the investigator to be possibly or probably related to each study treatment, and for serious adverse events. A patient's most severe event during each treatment regimen was used to define the intensity of the event. The difference in the incidence of treatment emergent AEs between Renagel® and calcium acetate was tested using the Fisher's exact test. Adverse events which started during the first treatment period, stopped prior to the second treatment period and restarted during the second treatment period were considered treatment emergent in both treatment groups.

Laboratory measures: Laboratory data were summarized for each study visit, for all changes between baseline and final, and for change between final visit and the end of the subsequent washout for both Renagel® and calcium acetate treatment. Wilcoxon signed rank tests were used to assess changed in laboratory values.

SUMMARY – CONCLUSIONS
Demographics and Renal History

The mean age of the patients was 55 years. Fifty-three percent of the patients were male and 46% were female. Fifty-six percent of the patients were African-American, 31% were Caucasian, 9% were Hispanic, 2% were Asian, and 1% were classified as "other" race. The primary cause of ESRD included hypertension (36%), diabetes (29%), nephritis (14%), polycystic kidney disease (4%) and "other" (18%).

Efficacy

Serum phosphorus: The mean baseline serum phosphorus level following two weeks of phosphate binder washout was 8.4 mg/dL for the Renagel® treatment group and 8.0 mg/dL for the calcium acetate treatment group and the mean change in serum phosphorus over the eight week treatment was -2.0 mg/dL ($p<0.0001$) for Renagel® treatment and -2.1 mg/dL ($p<0.0001$) for calcium acetate treatment. There was no difference between treatment groups in the change in serum phosphorus.

Serum calcium: The mean baseline serum calcium level following two weeks of phosphate binder washout was 9.1 mg/dL for the Renagel® treatment group and 9.1 mg/dL for the calcium acetate treatment group and the mean change in serum calcium over the eight week treatment period was 0.2 mg/dL ($p=0.0052$) for Renagel® treatment and 0.6 mg/dL ($p< 0.0001$) for calcium acetate treatment. The change in serum calcium from baseline to the end of treatment showed a difference between Renagel® and calcium acetate treatment ($p<0.0001$).

Incidence of hypercalemic events: For analyses where hypercalcemic events were defined as serum calcium levels greater than or equal to 10.4 mg/dL, 18.5% of patients had hypercalcemic events during Renagel® treatment and 45.1% of patients had hypercalcemic events during calcium acetate treatment. Additional analyses were performed for hypercalcemic events defined as serum calcium level greater than or equal to 11.0 mg/dL. In these analyses, 5% of patients had hypercalcemic events during Renagel® treatment and 22% of patients had hypercalcemic events during calcium acetate treatment. This difference was statistically significant ($p=0.0001$)

Serum intact PTH: The mean baseline serum iPTH level following two weeks of phosphate binder washout was 430.1 pg/mL for the Renagel® treatment group and 430.3 pg/mL for the calcium acetate treatment group and the mean change in serum iPTH over the eight week treatment was -48.2 pg/mL ($p=0.0068$) for Renagel® treatment and -100.6 pg/mL ($p<0.0001$) for calcium acetate treatment. There was no treatment difference in the change in iPTH between Renagel® and calcium acetate treatment ($p=0.17$).

Serum lipids: The mean baseline total cholesterol level following two weeks of phosphate binder washout was 173.3 mg/dL for the Renagel® treatment group and 167.2 mg/dL for the calcium acetate treatment group and the mean change in total cholesterol over the eight week treatment was 26.5 mg/dL ($p<0.0001$) for Renagel® treatment and 2.7 mg/dL ($p=0.2599$) for calcium acetate treatment. The change in total cholesterol was significantly different between treatments ($p<0.0001$).

The mean baseline LDL cholesterol level following two weeks of phosphate binder washout was 102.5 mg/dL for the Renagel® treatment group and 105.0 mg/dL for the calcium acetate treatment group and the mean change in LDL cholesterol over the eight week treatment was -25.3 mg/dL ($p<0.0001$) for Renagel® treatment and -4.1 mg/dL ($p=0.8394$) for calcium acetate treatment. This difference in change from baseline was statistically significant between treatment groups ($p<0.0001$).

There were no significant changes in HDL cholesterol or triglycerides with either Renagel® or calcium acetate treatment.

Safety Results

Adverse events: The incidence of treatment emergent adverse events was similar between Renagel® and calcium acetate treatment. Overall, 334 adverse events occurred among 64 patients (78.0%) during Renagel® treatment and 290 AEs among 65 patients (79.3%) during calcium acetate treatment ($p=1.00$). The body system with the most frequent adverse events was the “body as a whole” category, with 68 adverse events among 36 patients (43.9%) during Renagel® treatment and 65 adverse events among 38 patients (46.3%) during calcium acetate treatment ($p=1.00$). The only statistically significant treatment difference in adverse events occurred within the urogenital body system category. There were 14 urogenital body system events among 11 patients (13.4%) during Renagel® treatment versus one event among one patient (1.2%) during calcium acetate treatment ($p=0.0063$). However, only one of these events was judged to be related to Renagel® treatment (oliguria).

The incidence of treatment-related adverse events (adverse events judged as possibly or probably related to treatment) were largely similar between treatment groups. Overall, there were 47 treatment-related adverse events among 19 patients (23.2%) during Renagel® treatment and 18 treatment-related adverse events among 14 patients (17.1%) during calcium acetate treatment ($p=0.3833$). Most treatment-related adverse events were of mild intensity for both treatments. The digestive system category had the most treatment related adverse events with 35 events among 14 patients (17.1%) during Renagel® treatment and 10 events among 8 patients (9.8%) during calcium acetate treatment ($p=0.2101$). The most common digestive disorders were dyspepsia, diarrhea, and vomiting. Dyspepsia was more frequent during Renagel® treatment: 7 events among 7 patients (8.5%) during Renagel® treatment versus one event among one patient (1.2%) during calcium acetate treatment ($p=0.0703$).

There were 12 serious adverse events among 9 patients (11.0%) during Renagel® treatment and 9 serious adverse events among 7 patients (8.5%) during calcium acetate treatment. None of these events were judged to be related to treatment. Two patients died during the study; both patients died after calcium acetate treatment. The events were judged not to be related to calcium acetate treatment.

Laboratory values, physical exams and vital signs: Serum alkaline phosphatase increased significantly during Renagel® treatment (86 + 56 U/L to 114 + 73 U/L, $p<0.0001$) and did not change significantly with calcium acetate treatment. Serum 25 hydroxyvitamin D levels decreased from 27.8 + 17.6 ng/mL to 22.4 + 18.3 ng/mL during Renagel® treatment ($p<0.01$) and from 28.3 + 19.7 ng/mL to 23.6 + 16.3 ng/mL with calcium acetate ($p=0.03$), consistent with seasonal variation excepted in this trial. There were no other clinically significant changes in laboratory parameters.

There were no clinically significant changes in vital signs or physical exam abnormalities.

Based on Report Prepared on: 16 September 1997
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